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Captopril in combination with hydrochlorothiazide: Comparative efficacy *vs* perceived best therapy

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1 An open, randomized, multicentre, comparative trial on 2128 patients with mild-to-moderate hypertension, treated with so-called perceived best therapy or a combination of captopril plus hydrochlorothiazide (HCTZ), was conducted over a period of 10 weeks.
2 Both regimens lead to significant blood pressure reductions within the initial 6 weeks, with a difference of 3 mmHg systolic and 2 mmHg diastolic in favour of the captopril plus HCTZ regimen as compared to the perceived best therapy.
3 Both an increase in the daily dose of captopril in uncontrolled patients receiving initial treatment with captopril plus HCTZ and treatment with captopril plus HCTZ in uncontrolled patients receiving the perceived best therapy was followed by improved blood pressure control.
4 There were more withdrawals mainly due to side effects and non-compliance in the captopril plus HCTZ group as compared to the perceived best therapy group.
5 By contrast, there were fewer side effects and a tendency towards a more pronounced improvement of complaints and general well-being in the captopril plus HCTZ group.
6 The study has yielded no clear evidence of an increased number of side effects known to be associated with captopril.
7 Changes of the treatment regimen and dosages according to diastolic blood pressure during the study are difficult to achieve in a study of this type and size.

Keywords captopril hydrochlorothiazide hypertension

Introduction

Medical science organizations and experts have issued recommendations for antihypertensive drug therapy. Because of the steadily increasing number of new antihypertensive drugs available it is only natural that such recommendations for treatment of hypertension are subject to modifications with time. The selection of a new antihypertensive or the change of a commonly accepted stepped-care approach to antihypertensive therapy presupposes that the new preparation or regimen has proven superior, or at least equivalent, to the standard therapy. Thus, there is a need for studies involving sufficient patient numbers and conducted over an appropriate period of time to assess comparatively the hypotensive effect, the tolerance and the side effects of the new therapeutic regimen *vs* the standard treatment. An attempt has therefore been made

to evaluate the new combination of captopril and hydrochlorothiazide (HCTZ) within the scope of a comparative therapeutic trial conducted in a setting similar to everyday clinical practice which fulfills some of these methodological prerequisites.

Methods

The study design provided for a multicentre, randomized, open study involving 275 general practitioners and internists in private practice. There was no data auditing to assess if recruiting, randomization and follow-up of the patients followed the study protocol. The contribution of the authors to this study has been to prepare the study protocol, review the initial follow-up records for documentation problems, suggest possible improvements and analyse the results.

Criteria for inclusion and exclusion

Both previously treated and newly diagnosed, untreated hypertensive outpatients of both sexes beween 20 and 70 years of age were eligible for inclusion in the study. The blood pressure criterion was a diastolic blood pressure between 95 and 115 mmHg based on an average of four readings on two different days. All those included gave their consent after being informed as to the nature and purpose of the investigation. Withdrawal from the study was possible at any time without indication of reasons.

Relative and absolute contraindications to treatment with angiotensin-converting-enzyme inhibitors were mentioned in the protocol and excluded the patients from participation in the study.

Specifically, the following patients were excluded from the study: patients with hypertension in whom a change in the ongoing antihypertensive treatment was, in the opinion of the attending physician, unwarranted; patients with malignant hypertension; patients under treatment with diuretics, calcium antagonists or β-adrenoceptor blockers for other diseases; patients with serum creatinine levels above 1.5 mg 100 ml^{-1} or 130 $\mu mol\ l^{-1}$; patients with established hypersensitivity to captopril and/or thiazide diuretics as well as sulphonamides; patients with a total leucocyte count below 3000/mm^3; patients with autoimmune or collagen diseases, especially in cases of systemic lupus erythematosus, scleroderma and polyarteritis nodosa; patients treated with immunosuppressants, cytostatic drugs, allopurinol, nonsteroidal anti-inflammatory drugs or steroids; patients with hypokalaemia below 3.6 mmol l^{-1}; patients suffering from diseases with a poor prognosis; pregnant women and nursing mothers.

Definition of withdrawals:

Discontinuation of the study was recorded for one of the following reasons: increase of blood pressure above 120 mmHg despite regular taking of the drugs; prescription of antihypertensives for other reasons, e.g. β-adrenoceptor blockers or calcium antagonists for coronary heart disease or diuretics or vasodilators for heart failure; side effects occurring in presumptive or established connection with the study medication; pregnancy; other newly occurring, severe diseases; lack of willingness of the patient to continue participation in the study.

Blood pressure and heart rate were measured on entry into the study as well as 2, 4, 6, 8 and 10 weeks thereafter. At each visit the blood pressure was measured twice in the sitting position, using the same arm. All therapeutic decisions made during the study period were based on the mean diastolic value calculated from two measurements. Body weight and laboratory values for sodium, potassium, creatinine, uric acid, glucose, blood count and qualitative urinanalysis were determined upon onset of the study as well as after 6 and 10 weeks of therapy. At these same intervals the patients were asked to fill in a questionnaire containing 12 questions related to possible side effects, tolerance and general well-being and to grade these on a 5-step scale, with the best score being 1, the worst 5. For comparison of treatment groups mean values were calculated for each item.

Treatment schedule

Each physician participating in the study had to select one antihypertensive, i.e. either a single drug or a combination, which—according to his or her experience—represented the treatment of first choice for hypertension. This treatment method, in the following referred to as the 'perceived best therapy', was compared with a regimen based on a fixed combination of captopril plus HCTZ. Patients were allocated to the perceived best therapy group or treatment with captopril plus HCTZ by local randomization at a ratio of 2:3.

After inclusion in the study all patients first remained under random therapy for 6 weeks, i.e. either under the medication selected by the investigating physician or under captopril plus HCTZ at daily doses of 2 × 25 mg each (Figure 1). After 6 weeks the treatment was continued for an additional 4 weeks on the basis of the

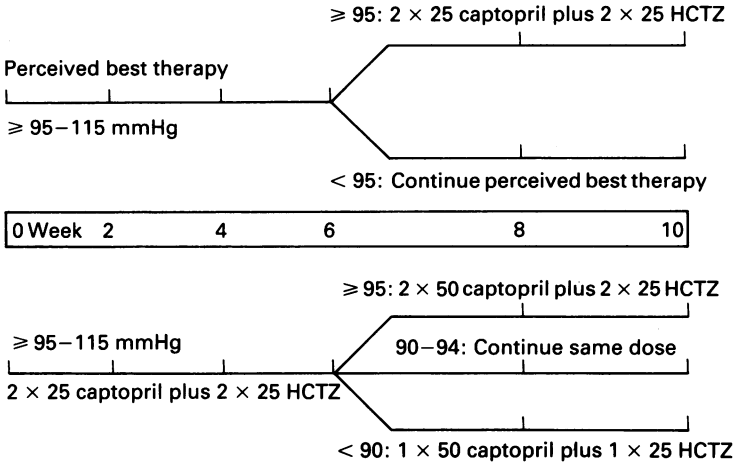

Figure 1 Treatment schedule at entry and change of therapy after 6 weeks according to diastolic blood pressure (HCTZ-hydrochlorothiazide).

diastolic blood pressure as follows:
(a) In the *perceived best therapy group*, the treatment remained unchanged for patients with blood pressures below 95 mmHg, whereas those with blood pressures of 95 mmHg or above were given the comparative medication, i.e. captopril plus HCTZ, 2 × 25 mg daily each.
(b) The *captopril plus HCTZ group* was further treated as follows: at blood pressures of 95 mmHg or above the dose of captopril was increased to 2 × 50 mg daily, whereas the dose of HCTZ was left unchanged, i.e. 2 × 25 mg daily; at blood pressures of 90 to 94 mmHg the regimen of captopril plus HCTZ remained unchanged, i.e. 2 × 25 mg daily each; at blood pressures below 90 mmHg the dose of HCTZ was reduced to 1 × 25 mg daily, whereas the daily dose of captopril was left unchanged; however, 1 × 50 mg was given instead of 2 × 25 mg.

Statistical methods

Multiple observations were analyzed with a repeated measures model followed by multiple test procedures. Student's *t*-tests were calculated to compare two sample means depending on the design with different groups or paired samples, and chi-square tests were performed for qualitative data.

Results

The study included a total of 2379 patients from 275 centres (Table 1). On examination of entry records, 251 patients were found to be ineligible in terms of age, blood pressure, leucocyte values, creatinine or potassium levels, leaving 2128 who fulfilled the entry criteria. 861 of them were randomly allocated to the perceived best therapy group and 1267 to the captopril plus HCTZ group. Thus, the ratio planned (2 to 3) was very close to the ratio achieved (2.04 to 3).

Table 1 Recruitment of patients

Number of centres	275
Number of patients recruited	2379
Number of patients ineligible	251
Number of patients included	2128
Randomized to perceived best therapy	861
Randomized to captopril plus HCTZ	1267
Ratio achieved	2.04:3
Ratio planned	2:3

The baseline data were similar in both groups (Table 2). This applies to sex ratio, age, body weight, percentage of patients with associated diseases and heart rate. It was also true for the systolic and diastolic blood pressure, which was 173/103 and 174/103 mm Hg in the perceived best therapy group and the captopril plus HCTZ group, respectively. However, the proportion of previously treated patients was significantly lower in the perceived best therapy group than in the captopril plus HCTZ group ($P < 0.05$).

The antihypertensive medication selected by the investigating physicians, i.e. the perceived best therapy, was dominated by β-adrenoceptor blockers (Table 3). More than half of all patients from this group were treated with β-adrenoceptor blockers—either by single-drug therapy (18.8%) or in combination with other antihyper-

Table 2 Baseline data at entry

	Perceived best therapy		*Captopril plus HCTZ*
Number of patients	861		1267
Mean systolic BP (mmHg)	173	N S	174
Mean diastolic BP (mmHg)	103	N S	103
Mean heart rate (beats min^{-1})	78.4	N S	77.5
Number of males	55.5%	N S	53.0%
Mean age (years)	53.9	N S	54.5
Mean body weight (kg)	77.3	N S	76.4
Associated disease	49.5%	N S	51.4%
Previously treated	54.8%	0.05	60.0%

Table 3 Antihypertensive drugs using in the perceived best therapy group

Drugs used	*Patients* n	%
β-adrenoceptor blockers—plus	309	35.9%
β-adrenoceptor blockers—mono	162	18.8%
Diuretics—mono	93	10.8%
Reserpine—plus	87	10.1%
Calcium antagonists—mono/plus	67	7.8%
Clonidine and methyldopa	54	6.3%
Vasodilators—mono/plus	24	2.8%
Other antihypertensives	65	7.5%
	861	100%

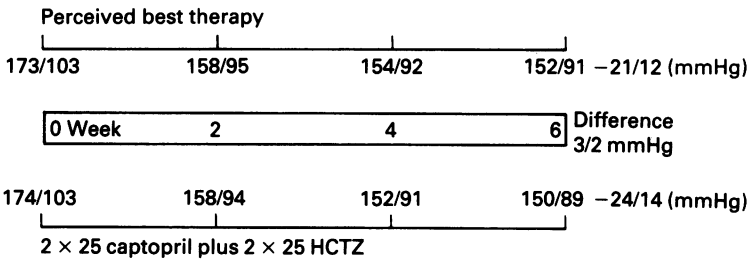

Figure 2 Blood pressures at entry and after 2, 4 and 6 weeks of treatment in patients receiving perceived best therapy or captopril plus hydrochlorothiazide (HCTZ)

tensives (35.9%). The proportion of monotherapy with diuretics amounted to 10.8%. Reserpine-containing compounds (which are still frequently used in Germany today) were given to 10.1% of the patients, calcium antagonists to 7.8%, clonidine or methyldopa to 6.3% and vasodilators to 2.8%. For the remaining 7.5% of patients other antihypertensives were prescribed.

Blood pressure control

A significant blood pressure reduction was achieved during the first 6 weeks in both groups (Figure 2). Compared to initial values of 173/103

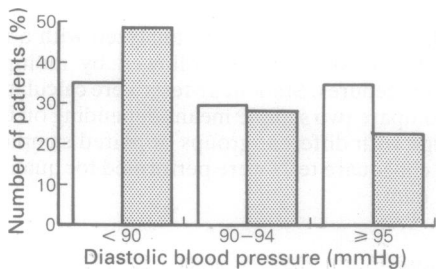

Figure 3 Patients (%) with diastolic blood pressures < 90, between 90 and 94 and ≥ 95 mmHg after 6 weeks of therapy with perceived best therapy (□) or captopril plus HCTZ (▦)

and 174/103 mmHg, reductions to 158/95 and 158/94 mmHg were obtained after 2 weeks, followed by 154/92 and 152/91 mmHg after 4 weeks, and 152/91 and 150/89 mmHg after 6 weeks of perceived best therapy and captopril plus HCTZ, respectively. In total, the blood pressure reduction after 6 weeks amounted to 21/12 and 24/14 mmHg ($P < 0.001$).

The differences between the two groups, amounting to 3 mmHg systolic and 2 mmHg diastolic in favour of the captopril plus HCTZ regimen, are small, but have clear effects on the responder rate (Figure 3). Blood pressure normalization to diastolic values below 90 mmHg was observed in 48.8% of the patients under captopril plus HCTZ, but only in 35.3% of those in the comparative group. The percentage of so-called non-responders, i.e. patients showing diastolic blood pressures of 95 mmHg or above after 6 weeks of therapy, was 34.9% in the perceived best therapy group but only 22.8% in the captopril plus HCTZ group.

The percentage of patients who had blood pressures of 95 mmHg or more even after 6 weeks of treatment and who thus needed higher doses or another kind of treatment varied according to the type of medication (Figure 4). The highest rates of patients with uncontrolled blood pressure were seen following treatment with reserpine-containing compounds (48.8%) and with clonidine or methyldopa (46.3%). This was followed by those under monotherapy with diuretics (41.1%), vasodilator containing compounds (34.3%), β-adrenoceptor blockers in combination with other drugs (32.8%), β-adrenoceptor blocker monotherapy (27.4%) and calcium antagonists (25.8%). Combined treatment with captopril plus HCTZ, 2 × 25 mg daily each, failed to yield blood pressure reduction below 95 mmHg within 6 weeks in only 22.8% of the patients.

Between week 6 and 10 a further blood pressure reduction was observed in both groups (Figure 5). In the *perceived best therapy group* (Figure 5, upper panel) the following changes were observed:

1. According to the protocol patients with a diastolic blood pressure of 95 mmHg or above after the initial 6 weeks were to be changed to the other treatment regimen. This was done in 162 patients with a blood pressure of 159/98 mmHg. After 4 weeks on captopril plus HCTZ the blood pressure was further reduced to 146/87 mmHg.
2. In total, 644 patients remained on the perceived best therapy, which should have been done according to the protocol in patients with diastolic blood pressure less than 95 mmHg after 6 weeks. Their blood pressure was 150/89 mmHg at week 6 and 147/89 mmHg after an additional 4 weeks.

The further blood pressure behaviour in the patients receiving *captopril plus HCTZ* (Figure 5, lower panel) can be summarized as follows:

1. In patients with uncontrolled hypertension, i.e. diastolic blood pressures of 95 mmHg or above, the captopril dose should have been doubled to 2 × 50 mg, whereas the HCTZ dose remained unchanged. This has been followed for 241 patients whose blood pressure was further reduced from 163/99 to 152/90 mmHg.

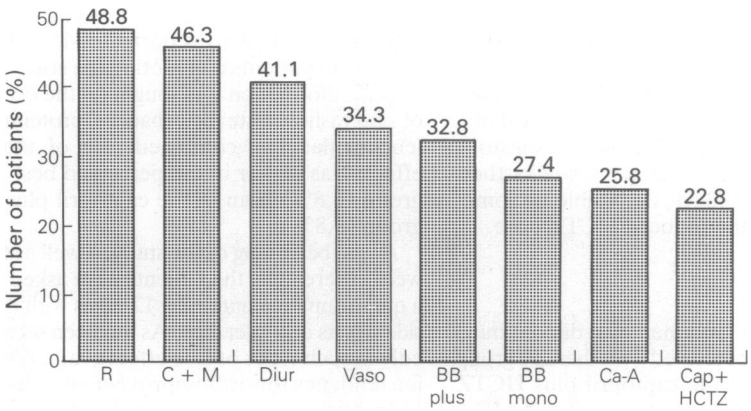

Figure 4 Patients (%) with diastolic blood pressures ≥ 95 mmHg (non-responders) after 6 weeks of therapy with various antihypertensive medications selected for the perceived best therapy and with captopril plus hydrochlorothiazide (R = reserpine; C + M = clonidine or methyldopa; Diur = diuretics; Vaso = vasodilators; BB plus = β-adrenoceptor-blockers in combination with other antihypertensives; BB mono = β-adrenoceptor blocker monotherapy; Ca-A = calcium antagonists, Cap + HCTZ = captopril plus hydrochlorothiazide)

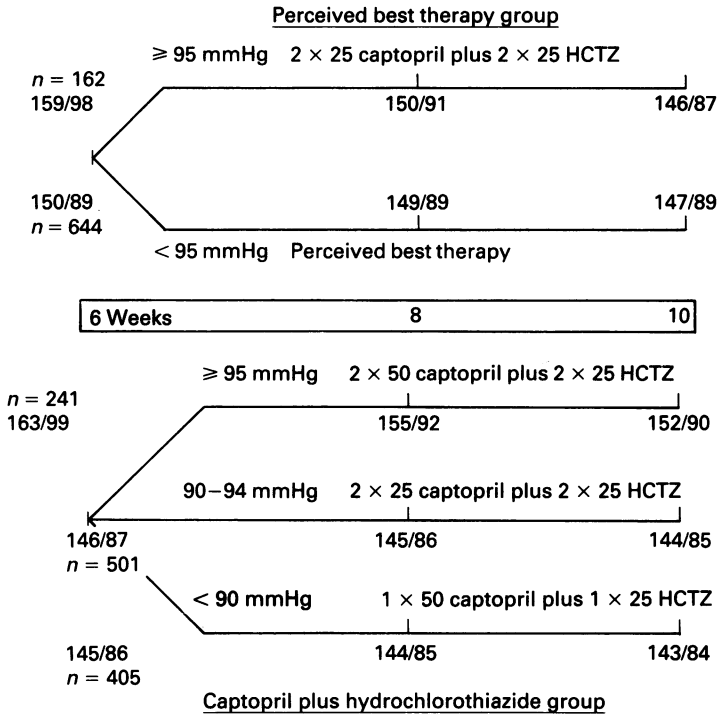

Figure 5 Blood pressures after 6 weeks of treatment in patients receiving perceived best therapy or captopril plus hydrochlorothiazide and after additional 2 and 4 weeks following continuation or change of therapy according to diastolic blood pressures at 6 weeks.

2. A total of 501 patients remained on the initial regimen and had stable or somewhat lower blood pressures after an additional 4 weeks, i.e. 146/87 and 144/85 mmHg, respectively.
3. The protocol prescribed that in patients with a diastolic blood pressure of less than 90 mmHg, the HCTZ dose should be reduced to 1 × 25 mg, with the captopril dose remaining unchanged but given as 1 × 50 mg instead of 2 × 25 mg daily. This was done in 405 patients with a diastolic blood pressure of 145/86. After 4 weeks their blood pressure was 143/84, i.e. stable or somewhat lower despite the reduced HCTZ dose.

Side effects

By the end of week 6, treatment was discontinued in 17 patients in the perceived best therapy group and in 62 patients of the captopril plus HCTZ group, corresponding to a rate of 2.0 and 4.9%, respectively (Table 4). The main reasons for withdrawals were side effects in 6 and 37 cases, corresponding to 0.7 and 2.9%, and non-compliance in 8 and 26 cases, i.e. 0.9 or 2.1%, in the perceived best therapy and captopril plus HCTZ group, respectively. The 37 patients on captopril plus HCTZ discontinuing treatment reported 52 side effects: 20 complained of gastrointestinal intolerance, 10 of skin rashes and 9 of dizziness and headache.

At the end of the study the investigating physicians were asked to report the side effects of therapy in patients completing the study. In particular, information was sought on the occurrence of skin rashes, taste disturbances, proteinuria and leucopenia. The combined rate of these side effects was higher in the perceived best therapy group (3.8%) than in the captopril plus HCTZ group (2.8%).

At the beginning of the study as well as 6 and 10 weeks thereafter, the patients were asked to fill in a questionnaire containing 12 items with regard to side effects and tolerance. As has been seen repeatedly in such types of side effect evaluation, there is a tendency towards improvement independent of treatment regimen, even in placebo groups. This was also true for the perceived best therapy group and the captopril plus HCTZ group to different degrees, the only exception being skin rashes in the perceived best therapy group. In comparing the two treatment groups the differences in the mean changes between entry of

Table 4 Withdrawals from therapy during the first 6 weeks of therapy

	Perceived best therapy			*Captopril plus HCTZ*	
	n	*Rate*	P	n	*Rate*
Number of patients	861			1267	
Patients withdrawn	17	2.0%	0.01	62	4.9%
—Side effects	6	0.7%	0.01	37	2.9%
—Non-compliance	8	0.9%	0.05	26	2.1%
—New disease	2		NS	4	
—Other causes	2		0.05	12	

Table 5 Mean scores at entry and after 6 weeks of treatment according to a questionnaire related to possible side effects, tolerance and general well-being using a 5 step scale (the best score being 1, the worst 5)

	Perceived best therapy		*Captopril plus HCTZ*		*Difference of changes*	
	At entry	*6 weeks*	*At entry*	*6 weeks*		
Headache	2.80	2.16	2.78	1.96	0.18	0.001
Sleep	2.75	2.28	2.80	2.10	0.23	0.001
Dry mouth	1.74	1.70	1.82	1.54	0.24	0.001
Fatigue	2.73	2.27	2.79	2.03	0.30	0.001
Nausea	1.68	1.58	1.75	1.44	0.21	0.001
Sense of taste	1.30	1.26	1.40	1.27	0.09	0.05
Rash	1.17	1.17	1.23	1.19	0.04	NS
Oedema	1.71	1.47	1.74	1.36	0.14	0.01
Dizziness	2.67	2.15	2.73	1.93	0.28	0.001
Awareness	2.68	2.25	2.72	2.05	0.24	0.001
Sexual function	2.16	2.09	2.27	1.89	0.31	0.001
Well-being	2.78	2.28	2.79	2.00	0.29	0.001

study and after 6 weeks of treatment were calculated (Table 5). With the exception of skin rashes the improvement for all other items was significantly more pronounced for the captopril plus HCTZ regimen as compared to the perceived best therapy. The score for fatigue, dizziness, sexual function and general well-being showed differences of over 0.25.

Laboratory data

The mean values initially established for sodium, potassium, creatinine, uric acid, glucose, and haemoglobin did not change in either group after 6 and 10 weeks of treatment. The leucocyte values were not different between the perceived best therapy and captopril plus HCTZ. However, there was a significant fall in the captopril plus HCTZ group at 6 and 10 weeks compared with the counts at entry (Table 6).

There was no difference in the percentage of patients with a positive dip test for proteinuria at entry and after 6 weeks of treatment (Table 6). However, there was a significant difference after 10 weeks between the perceived best therapy and captopril plus HCTZ, 3.3% and 5.9% respectively ($P < 0.05$). The figure of 5.9% is the mean value calculated on the basis of 5.1% for all patients on captopril plus HCTZ since initiation of the study and a figure of 8.8% for patients changed from the perceived best therapy to the captopril plus HCTZ regimen after 6 weeks.

According to the protocol, no patients with creatinine values above 1.5 mg 100 ml^{-1} or leucocyte values less than 3000/mm^3 were included in the study. In searching for patients who developed these values during the study there were no major differences between the two groups either for creatinine values above 1.5 mg 100 ml^{-1} or for leucocyte values less than 3000/mm^3 at 6 and 10 weeks (Table 6), the exception being serum creatinine values above 1.5 mg 100 ml^{-1} at week 10. However, the numbers are small and require very cautious interpretation.

Discussion

Several new antihypertensive agents have been introduced during the past decade that offer many options for the treatment of hypertension. However, in comparative trials any new drug or regimen should be tested against the commonly accepted standard therapy in terms of efficacy, tolerance and side effects.

The present study, which attempted to fulfill some of these requirements, has a number of advantages. First of all, it provides for a setting

Table 6 Laboratory data at entry and after 6 and 10 weeks of treatment

		Perceived best therapy			*Captopril plus HCTZ*	
		n	*Rate*	P	n	*Rate*
Proteinuria	Week 0	54	6.5%	NS	91	7.5%
	Week 6	47	5.7%	NS	66	5.6%
	Week 10	21	3.3%	0.05	74	5.9%
Serum-creatinine	Week 0	0	0	—	0	0
> 1.5 mg 100 ml^{-1}	Week 6	3	0.36%	NS	4	0.34%
	Week 10	2	0.31%	0.05	12	0.90%
Leucocytes	Week 0	0	0	—	0	0
< 3000/mm^3	Week 6	2	0.24%	NS	0	0
	Week 10	1	0.16%	NS	2	0.15%
Leucocytes	Week 0	6540	—	NS	6641	—
(cells/mm^3)	Week 6	6554	—	NS	6486*	—
	Week 10	6520	—	NS	6488*	—

* = $P < 0.01$ at weeks 6 and 10 as compared to week 0

similar to everyday clinical practice to compare the new combination of captopril plus HCTZ with an antihypertensive medication considered to be the treatment of first choice by the investigating physicians. The study is randomized and includes more than 2000 patients. On the other hand, it is an open study conducted over a period of only 10 weeks without data auditing to assess if recruiting, randomization and follow-up of the patients followed the study protocol.

Diuretics result in stimulation of the renin-angiotensin system, while angiotensin-converting-enzyme (ACE) inhibitors prevent the conversion of angiotensin I into the vasopressor substance angiotensin II. Therefore, from a theoretical point of view the concurrent administration of both substances in antihypertensive therapy would appear to make good pathophysiological sense. Several studies have confirmed this hypothesis, demonstrating a good antihypertensive effect of the combination of captopril plus HCTZ (Andersen *et al.*, 1986; Creisson *et al.*, 1986; Lederle, 1985; Weinberger, 1983). In the present study this combination proved at least as good or slightly better than the perceived best therapy. The small difference of 3 mmHg systolic and 2 mmHg diastolic in favour of the combination was clearly reflected in the rate of blood pressure normalization to below 90 mmHg (48.8 *vs* 35.3%) and the rate of non-responders (22.8 *vs* 34.9%). Comparison with the individual substances and combinations of the perceived best therapy revealed some notable differences: while reserpine combinations failed to lower the blood pressure below 95 mmHg in almost every second patient, the non-responder rate for the combination of HCTZ and captopril was only 22.8% and thus slightly lower than for therapy with β-adrenoceptor blockers (32.8 and 27.4%) and calcium antagonists (25.8%).

Evidently, the protocol instructions regarding the change of both therapeutic regimen and dosage after 6 weeks of initial treatment on the basis of the diastolic blood pressure were either too difficult to understand or poorly feasible under practical clinical conditions. There was a clear tendency to continue the initial treatment irrespective of the diastolic blood pressure after 6 weeks. For example, in the captopril plus HCTZ group only 342 patients had a diastolic blood pressure of 90 to 94 mmHg, yet 501 patients were kept on the initial therapy. This accounts for a mean diastolic blood pressure of 87 mmHg in a group of patients whose diastolic pressure should have been 90 to 94 mmHg.

Nevertheless, evaluation of the results of continued therapy between weeks 6 and 10 showed that:

1. patients with uncontrolled hypertension receiving the perceived best therapy experienced a further marked reduction in blood pressure from 159/98 to 146/87 mmHg after being switched to captopril plus HCTZ.
2. In the case of inadequate blood pressure reduction during captopril plus HCTZ therapy an increase in the captopril component from 2×25 to 2×50 mg day^{-1} with an unchanged HCTZ dose resulted in a marked blood pressure reduction from 163/ 99 to 152/90 mmHg.
3. In the case of blood pressure normalization within 6 weeks in the combination group, the blood pressure remained constant or even under-

went a further slight drop between the 6th and 10th week (145/86 and 143/84 mmHg) when the HCTZ dose was reduced from 2 × 25 to 1 × 25 mg with the captopril dose left unchanged (1 × 50 instead of 2 × 25 mg).

Another important aspect of the present study concerns withdrawals, side effects and tolerance. Some surprising, in part contradictory, findings are noteworthy in view of the large number of 2000 patients involved. The withdrawal rate, mainly due to side effects and non-compliance, was higher by a factor of almost 2.5 in the captopril plus HCTZ group than in the perceived best therapy group. This difference was present for both previously treated and untreated patients. However, in contrast to the rate of discontinuation, the rate of side effects according to the information given by the investigating physicians for patients completing the study was higher in the perceived best therapy group (3.8%) than in the captopril plus HCTZ group (2.8%). Furthermore, it should be noted that skin rashes, taste disturbances, and hypotension, i.e. side effects shown by experience to be associated with the administration of angiotensin-converting-enzyme inhibitors (Heel *et al.*, 1980) did not occur more often under captopril plus HCTZ therapy than under the comparative treatment.

Most laboratory values did not change during the study. Most notably, this also applies to serum potassium, urea and creatinine, which did not change significantly during treatment with the diuretic-containing combination with captopril. The serum creatinine rose to over 1.5 mg 100 ml^{-1} in two patients of the perceived best therapy group and in 12 patients of the captopril plus HCTZ group. This corresponds to rates of 0.31 and 0.90% ($P < 0.05$). All in all, the case numbers are very small and require cautious interpretation.

Leucopenia and proteinuria have been described as side effects of captopril (Heel *et al.*, 1980). In the present study there was no difference between the perceived best therapy and the captopril plus HCTZ regimen in terms of the total leucocyte count and the rate of patients with a leucocyte count below 3000 mm^3 after 6 and 10 weeks of therapy. However, in the captopril plus HCTZ group after 6 and 10 weeks a significant reduction in the leucocyte count from 6641 to 6486 mm^3—well within the normal range—was noted.

At the beginning of the study and after 6 weeks the proteinuria rate was identical in the two groups (Table 6). Only after 10 weeks was there a statistically significant difference with a rate of 3.3% for the perceived best therapy and 5.9% for captopril plus HCTZ ($P < 0.05$). One gets the impression that—by chance or intention—a major portion of patients with proteinuria receiving the perceived best therapy were changed to captopril plus HCTZ, leaving behind a low figure for proteinuria in the perceived best therapy group at 10 weeks.

In a multicentre randomized double-blind study including 626 men with mild hypertension captopril proved superior to methyldopa and propranolol in terms of certain criteria bearing on the quality of life (Croog *et al.*, 1986). Patients taking captopril, as compared to methyldopa, scored significantly higher on measures of general well-being, work performance, visual-motor function and life satisfaction and had fewer side effects. Compared to patients taking propranolol, they reported fewer side effects, less sexual dysfunction and greater improvement in measures of general well-being. It is interesting to note that in the present open study patients treated with the captopril plus HCTZ combination scored significantly better in 11 out of 12 different criteria than those receiving the perceived best therapy. The differences were statistically significant and were especially apparent in the responses to questions concerning fatigue, dizziness, sexual function and general well-being.

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